REMARKS

The claims in the application are 2 and 4-22. The Claims 1 and 2 had been rejected under 35 USC112, 2nd paragraph, as indefinite. Claim 1 has been cancelled; and Claim 2 amended to set forth the step involved in the process. Reconsideration and withdrawal of this rejection is respectfully requested.

The Claims 23-26 had been rejected under 35 USC112, 2nd paragraph, as indefinite. These claims have been cancelled, and reconsideration and withdrawal of this rejection is respectfully requested.

All claims had been rejected, under both 35 USC102 and /or 103, based on the Kesteleyn et al. reference US 7,126,015. Reconsideration and withdrawal of this rejection is respectfully requested for the following reasons. Applicants respectfully disagree with the Examiner's assertions that replacing the mixture of epimers of intermediate compounds of formula (4), hereinafter referred to as compound (4), by the single alpha epimer of the methyl acetal form of intermediates of formula (4), is to be considered a routine and obvious modification. Claim 2 as currently amended describes a method for the preparation of (3R,3aS,6aR) hexahydro-furo[2,3-b]furan-3-ol, hereinafter referred to as compound (6), using (3aR,4S,6aS) 4-methoxy-tetrahydro-furo[3,4-b]furan-2-one, hereinafter referred to as alpha-(4). While Kesteleyn et al. describes the synthesis of compound (6), this synthesis starts from a 2,3-diprotected-2,3-dihydroxy-propionaldehyde that is transformed into a derivative encompassing a nitromethyl and one or two carboxylate moieties. The derivative is subsequently transformed by a Nef reaction into a compound (4), which is reduced and submitted to an intramolecular cyclization reaction to obtain compound (6). The Kesteleyn process uses a mixture of epimers of compound (4), i.e. (3aR,4S,6aS) and (3aR,4R,6aS), rather than the particular epimer in the present invention.

The advantage of using of the particular alpha-(4) epimer of the methyl acetal form of intermediates of formula (4) instead of a mixture of epimers of compound (4) in Kesteleyn et al., is that the synthetic procedure becomes much more suitable for industrial scale due to the intermediate purification step that is amenable to industrial scale.

Surprisingly, it has been found that - contrary to epimeric mixtures of intermediates of formula (4) - the alpha-epimer of the methyl acetal form of intermediates of formula (4) can be

isolated and purified by crystallization. One of the drawbacks of the method for the preparation of (6) as disclosed by Kesteleyn et al., is the lack of appropriate intermediate compound purification. In the absence of intermediate compound purification, impurities are accumulated in the preparation of compound (6), which in itself is a key intermediate in the synthesis of retroviral protease inhibitors, and, for which no convenient industrial scale purification method is available. Due to the fact that alpha-(4) can be isolated by crystallization in quantitative yields, the use of alpha-(4) in the synthesis of (6) allows for an intermediate compound purification step on an industrial scale, thereby enhancing or optimizing the overall synthetic procedure.

In the reference Kesteleyn et al.patent, the stereochemistry at the MeO-group position of intermediate compound (4) was not considered relevant to the preparation of the final compound (6) since it did not affect the stereochemistry of the target compound (6) in the subsequent synthetic steps. Therefore, based on the teachings of the prior art and in the absence of the availability of intermediate alpha-(4) (along with the knowledge of its advantageous properties) at the time of filing of the present invention, the skilled person had no incentive to modify the Kesteleyn et al.method accordingly.

Applicant submits that the use of the particular stereoisomer alpha-(4) instead of the mixture of epimers of intermediate compounds of formula (4) is not an obvious modification of the method disclosed by Kesteleyn et al..

Respectfully submitted,

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